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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,220	07/14/2003	Nicholas M. Dean	ISPH-0751	7005

7590 04/20/2005

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/619,220	DEAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78,79 and 81-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78,79 and 81-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 78-79 and 81-80 are pending in this application and are currently under examination. Claim 80 has been cancelled.

Response to Arguments

The rejection of claims 78-84 under 35 U.S.C. 112, paragraph 1 written description, as set forth in the Office action mailed 11/01/2004, has been withdrawn in response to Applicant's amendment to the claims filed 02/01/2005.

The rejection of claims 78-84 under 35 U.S.C. 112, paragraph 1 enablement, as set forth in the Office action mailed 11/01/2004, is maintained. Applicant' arguments filed 02/01/2005 have been fully considered but they are not persuasive.

Applicant argues, "...the number of companies and individual researchers focused on the study of antisense oligonucleotides as therapeutic agents clearly demonstrates that those skilled in the art believe that they are useful as therapeutic agents." Applicant states that the claims as amended recite an antisense compound that binds to Fas and further states "[a]n antisense oligonucleotide targeted to this portion of Fas has been demonstrated to inhibit tissue injury in an ischemic reperfusion model *in vivo*." Applicants point out that "[t]he written description requirement does not require demonstration that a compound work for the method claimed. Instead, the specification must provide a reasonable expectation that the claimed method would

work. The extensive knowledge of those skilled in the art regarding the mechanism of action of Fas and antisense oligonucleotides provides sufficient support for the methods claimed."

The arguments have been considered but are not persuasive because as detailed in the previous Office Action filed 11/01/2004, the state of the art for therapeutic *in vivo* applications using antisense is unpredictable despite the belief that antisense oligonucleotides are useful as therapeutic agents.

As cited in the previous Office Action, Jen *et al.*, states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column).

Further, as evidence of the state of the art for antisense therapeutics, post-filing art confirms that therapeutic *in vivo* applications using antisense is still very unpredictable as summarized by Caplen (Expert Opin. Biol. Ther. 2003, 3(4): 575-586) who states "[t]he key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system, have been problems the gene therapy field has struggled with for over a decade now" (see page 581, last paragraph).

Schiavone et al. (Current Pharmaceutical Design, 2004, Vol. 10: 769-784) states "[d]espite promising futures, antisense-based therapeutics are far from being an established reality" (see page 769, abstract). Schiavone et al. further states that "[d]espite the success

obtained in in vitro studies, the development of antisense drugs has met obstacles in the clinical field where results are far from satisfactory" (see page 780, column 1).

Therefore, in view of the unpredictability in the art of antisense-based therapy, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Applicant further argues that "...Fas is a secreted protein that results in tissue damage by forming a cross-linked product with FasL. Moreover, the Fas need not be provided by the tissue undergoing...ischemia, but instead can be provided by infiltrating inflammatory cells....Therefore, the demonstration of the inhibition of ischemia reperfusion injury in a single tissue type is sufficient to predict efficacy in other tissue types."

The claims are broadly drawn to a method of preventing ischemia reperfusion injury in any cardiac, renal, hepatic or skin allograft recipient comprising administering any antisense targeted to the mouse Fas gene. The specification does not teach a decrease in Fas expression in infiltrating inflammatory cells after administration of any antisense compound.

Further, example 20 of the specification as filed teaches a mouse antisense model with an ischemia reperfusion injury of the kidney and a correlation between administration of a mouse antisense compound and a decrease in apoptosis of the tubular cells of the kidney as well as decreased levels of Fas mRNA expression in the tubular cells of the kidney. The specification does not teach that because of administration of an antisense compound to murine kidney cells, there is a decrease in Fas expression in infiltrating inflammatory cells and therefore prevention of ischemia reperfusion in cardiac, renal, hepatic or skin tissue types.

Given the teachings of the specification as discussed above and in the previous Office action filed 11/01/2004, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly disclosed methodologies of the instantly claimed invention, would result in successful inhibition of Fas and further prevention of ischemia reperfusion injury in any cardiac, renal, hepatic or skin allograft recipient. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

This action is FINAL.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached at 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are

available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
Examiner
Art Unit 1635

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